

Notice of Allowability

Application No.

09/742,008

Examiner

Chih-Min Kam

Applicant(s)

VISKOV, CHRISTIAN

Art Unit

1656

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to 11/14/06.
2. ☒ The allowed claim(s) is/are 1,5-13,23 and 24.
3. ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some* c) ☐ None of the:
- ☒ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

* Certified copies not received: _____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.

THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

4. ☐ A SUBSTITUTE OATH OR DECLARATION must be submitted. Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL PATENT APPLICATION (PTO-152) which gives reason(s) why the oath or declaration is deficient.
5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
- (a) ☐ including changes required by the Notice of Draftsperson's Patent Drawing Review (PTO-948) attached
- 1) ☐ hereto or 2) ☐ to Paper No./Mail Date _____.
- (b) ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.
- Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).
6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

- | | |
|--|---|
| 1. <input type="checkbox"/> Notice of References Cited (PTO-892) | 5. <input type="checkbox"/> Notice of Informal Patent Application |
| 2. <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 6. <input type="checkbox"/> Interview Summary (PTO-413),
Paper No./Mail Date _____ |
| 3. <input type="checkbox"/> Information Disclosure Statements (PTO/SB/08),
Paper No./Mail Date _____ | 7. <input checked="" type="checkbox"/> Examiner's Amendment/Comment |
| 4. <input type="checkbox"/> Examiner's Comment Regarding Requirement for Deposit
of Biological Material | 8. <input checked="" type="checkbox"/> Examiner's Statement of Reasons for Allowance |
| | 9. <input type="checkbox"/> Other _____ |

DETAILED ACTION

Status of the Claims

1. Claims 1, 5-13, 23 and 24 are pending.

Applicants' amendment filed November 14, 2006 is acknowledged. Applicants' response has been fully considered. Claims 1 and 13 have been amended. Claims 15-21 have been cancelled in the Examiner's amendment (See below). Therefore, claims 1, 5-13, 23 and 24 are examined.

Withdrawn Claim Rejections - 35 USC § 112

2. The previous rejection of claims 1 and 5-12, under 35 U.S.C. 112, second paragraph, is withdrawn in view of applicants' amendment of the claim, and applicants' response at pages 9-10 in the amendment filed November 14, 2006.

Withdrawn Claim Rejections - 35 USC § 103

3. The previous rejection of claims 13, 23 and 24 under 35 U.S.C. 103(a) as being unpatentable over Barriere *et al.* (U. S. Patent 5,994,299) in view of Seebach *et al.* (Helvetica Chimica Acta 76, 1564-1590 (1993)) and Gordon *et al.* (U. S. Patent 5, 559,256), is withdrawn in view of applicant's amendment to the claims, and applicant's response at pages 10-13 in the amendment filed November 14, 2006.

Examiner's Amendment

An **Examiner's Amendment** to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 CFR 1.312. To ensure consideration of such an amendment, it **MUST** be submitted no later than the payment of the issue fee.

Examiner's Amendment to the Specification:

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Please replace the paragraph at page 1, lines 1-3 with the following paragraph:

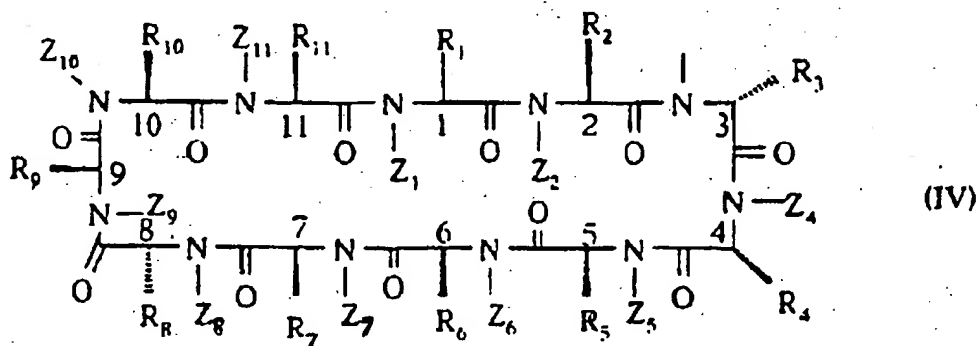
This application is a continuation of International Application No. PCT/FR99/01480, filed June 21, 1999, published as WO 99/67280 on December 29, 1999, which claims priority of French Patent Application 98/07,846, filed June 22, 1998.

Examiner's Amendment to the Claims:

Please cancel claims 15-21.

Claim 13 has been amended as follows:

13. (Currently amended) A process for preparing a cyclosporin derivative substituted at the 3-position, said process comprising preparing a polyanion by treating a cyclosporin with a hexamethyldisilazane metal salt, optionally in the presence of a metal halide, wherein the treatment of the cyclosporin is carried out at a temperature ranging from -40°C to 0°C, adding an electrophilic agent to said treated cyclosporin, and, optionally converting the product of said addition to a salt, in which at least one obtained cyclosporin derivative substituted at the 3-position has the formula:



in which

the radicals R_1 , R_2 , and R_4 to R_{11} , and Z_1 , Z_2 , and Z_4 to Z_{11} are defined as for cyclosporin A, with the exception of R_4 and Z_4 , which are defined so as to have, at the 4-position, the amino acid 4'-hydroxy-methyllucine, and of R_3 , which is -S-OH₃ or a radical -S-Alk-R° in which:

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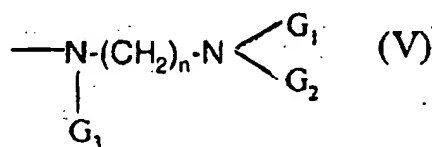
Alk is an alkylene radical comprising from 2 to 6 straight- or branched-chain carbon atoms or a cycloalkylene radical comprising from 3 to 6 carbon atoms;

and

R° is

a hydroxyl, carboxyl, or alkyloxycarbonyl radical; or

an -NG₁G₂ radical or a radical of formula:



in which G₁ and G₂, which are identical or different, are each a hydrogen atom; or

a phenyl, cycloalkyl (C₃₋₆), alkenyl (C₂₋₄), or alkyl radical, each of which is optionally substituted by a halogen atom, an alkyloxy, alkyloxycarbonyl, amino, alkylamino, or dialkylamino radical; or

a benzyl radical or a saturated or unsaturated heterocyclyl radical comprising 5 or 6 ring members and from 1 to 3 heteroatoms; or

G₁ and G₂ form, with the nitrogen atom to which they are attached, a saturated or unsaturated heterocycle comprising from 4 to 6 ring members which can comprise another heteroatom chosen from nitrogen, oxygen, and sulphur and which is optionally substituted by alkyl, phenyl, or benzyl; and

G₃ is a hydrogen atom or an alkyl radical, and n is an integer from 2 to 4,

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the alkyl portions or radicals defined above are straight or branched and
comprise from 1 to 4 carbon atoms.

The following is an Examiner's Statement of Reasons for Allowance: The following references appear to be related to the claimed invention. Barriere *et al.* (U. S. Patent 5,994,299) disclose preparation of [4'-hydroxy-MeLeu]⁴-cyclosporin compounds of general formula (I) by treating the cyclosporine of formula (II) (having Sar at position 3) with a lithium derivative such as n-butyllithium, lithium diisopropylamide or a mixture to activate sarcosine at the 3-position at temperature of -70 °C to -78 °C; and then reacting with a disulfide (i.e., R-Alk-S-S-Alk-R), where the group at 3-position is -S-Alk-R; Seebach *et al.* (Helvetica Chimica Acta 76, 1564-1590 (1993)) disclose an enolate of cyclosporine A including sarcosine enolate can be formed when cyclosporine A is treated with lithium diisopropylamide (LDA), where the deprotonation at sarcosine occurs, and the alkylation product can be detected after reacting with an alkylating agent; and Gorden *et al.* (U. S. Patent 5,559,256) disclose the protected amino ester LXVIII can be alkylated via its enolate anion, which is formed by treatment of the ester with a base such as lithiumdisoporpylamide or lithium bis(trimethylsilyl)amide. However, these references either alone or in combination do not teach or suggest a method of preparing a cyclosporin derivative substituted at the 3 position by preparing a polyanion using a hexamethyldisilazane metal salt. Therefore, the claims are allowable over the art of record.

Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chih-Min Kam whose telephone number is (571) 272-0948. The examiner can normally be reached on 8.00-4:30, Mon-Fri.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen Bragdon can be reached at 571-272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Chih-Min Kam, Ph. D.
Primary Patent Examiner



CHIH-MIN KAM
PRIMARY EXAMINER

CMK

January 24, 2007